

Letter to the Editor

Accuracy of human papillomavirus testing in primary screening of cervical neoplasia: Results from a multicenter study in India

Michelle J. Khan^{1,2*}, Mark Schiffman¹ and Jose Jeronimo¹

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA

²Howard Hughes Medical Institute, Chevy Chase, MD, USA

Dear Sir,

The article by Sankaranarayanan *et al.*¹ reported the results from 4 cervical cancer screening projects performed in 3 different regions in India. Their study of 18,085 previously unscreened women aged 25–65 years compared the effectiveness of 4 screening strategies: human papillomavirus (HPV) DNA testing, conventional Papanicolaou cytology, visual inspection after the application of acetic acid (VIA) and Lugol's iodine (VILI). Our concern is not about the study itself, but about possible over-concern by readers regarding the mediocre performance of HPV testing compared to the other screening techniques (particularly VILI) and compared to other reports on the efficacy of HPV testing in the literature. Specifically, Sankaranarayanan *et al.*¹ observed HPV test sensitivities in their 4 projects ranging from only 45.7–80.9% for detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+). In contrast, research studies have estimated sensitivity for detection of CIN2+ of >85% for HPV testing.^{2–4} When considering the possible usefulness of HPV testing in India and what practical effectiveness (as opposed to theoretical efficacy) could be achieved, readers should carefully consider caveats mentioned but perhaps not sufficiently emphasized by the authors.

First, readers should take note that the project was a study of effectiveness using briefly-trained local personnel during the early phases of introduction of new technology. Sankaranarayanan *et al.*¹ trained local health workers to collect cervical specimens for conventional cytology and for HPV DNA testing, to provide VIA and VILI and to treat lesions by cryotherapy. But training and quality monitoring were not at all intensive or prolonged. Data collection was not delayed to permit a "learning curve." Nonetheless, the best-performing center in Trivandrum achieved good HPV test performance (80.9% sensitivity), which might be replicable elsewhere in India.

Second, readers should note that, as the authors recognize, the reference standard of disease based on local colposcopy was imperfect and variable. It might seem paradoxical that in an effectiveness study meant to assess real-life performance of screening assays, the diagnosis of disease must still be as accurate as possible. Even if subsequent disease diagnosis in the community will not be as intensive, misclassification of disease when evaluating a new test can lead to false conclusions. As a surrogate for prevention of invasive cervical cancers, Sankaranarayanan *et al.*¹ relied on local colposcopy and guided biopsies for all 18,085 women. They assessed the reliability of this reference standard by reviewing 182 histology slides with a categorical outcome grouping normal, inflammation, atypia, and CIN1 as one category and CIN2, CIN3 and invasive cancer as the second category. This approach, although uniform and

seemingly complete, might lead some readers to believe incorrectly that verification bias was completely addressed.

In fact, colposcopic assessment and guided biopsy even among experts is inaccurate and very unreliable, failing to detect approximately one-third of small CIN3 lesions.⁵ Moreover, differential bias is possible when evaluating different kinds of screening tests. The choice of colposcopy and directed biopsy as a reference standard when comparing VILI, VIA, cytology and HPV testing raises to an unknown degree the estimated accuracy of screening with visual methods that resemble colposcopy itself, because visual approaches all have correlated errors. Conversely, reliance on a colposcopic biopsy standard tends to decrease the estimated accuracy of HPV DNA screening; women with CIN3+ and a positive HPV test but normal colposcopy are counted as false positive HPV tests, rather than false negative colposcopies. Correspondingly, Sankaranarayanan *et al.*¹ showed that HPV test performance was highest at Trivandrum, where a lower percentage of normal colposcopies (57.5% compared to >70% at the other 3 sites) led to a larger number of women receiving guided biopsies, so that the reference standard was probably most accurate.

We believe that HPV testing, along with other methods, could eventually be applied widely even in low-resource regions. The choice of when and how to apply HPV testing will be regional, and combinations of HPV testing and cytology or HPV and visual methods will be used based on local competences and cost. Early effectiveness data on HPV that fail to approach our hopes of efficacy should simply refine our search for the most robust technology and training methods.

Yours sincerely,

Michelle J. KHAN, Mark SCHIFFMAN, and Jose JERONIMO

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*Correspondence to: 6120 Executive Blvd., EPS Room 7101, Rockville, MD 20852. Fax: +301-402-0916. E-mail: khanmi@mail.nih.gov
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